

QnAs with Stephen G. Young

Julia Sklar, Science Writer

For more than half a century, a mystery shrouded the enzyme that breaks down triglycerides in the bloodstream: How does the enzyme, lipoprotein lipase, get from the interstitial spaces to its site of action inside blood vessels? This mystery intrigued Stephen G. Young, a cardiologist at the University of California, Los Angeles. Through more than 15 years of research, Young and his University of California, Los Angeles faculty collaborators, Loren Fong and Anne Beigneux, uncovered a protein called GPIHBP1 that not only captures and moves lipoprotein lipase into blood vessels but stabilizes the enzyme as well. Understanding how GPIHBP1 works allowed Young and colleagues to solve the structure of lipoprotein lipase and to identify a treatment for a subset of patients with severe hypertriglyceridemia (chylomicronemia), a disorder in which the body's ability to break down fats is impaired, often leading to acute pancreatitis. In his Inaugural Article (1), Young reviews the long arc of his research on this important protein and its role in the metabolism of plasma triglycerides. PNAS recently spoke with Young about this work.

PNAS: Take us through the process of getting to know GPIHBP1. Where did your drive to better understand this protein begin?

Young: Lipoprotein lipase was characterized in the 1950s and studied extensively. But it was mysterious how this enzyme, which is made and secreted by myocytes and adipocytes, reached the inside of blood vessels. Indeed, it was a mystery for so long that most scientists had forgotten that it was a mystery. How lipoprotein lipase entered blood vessels was rarely discussed at scientific meetings.

We [Young, Fong, and Beigneux] were lucky to hear from a colleague at Genentech about very high triglyceride levels in mutant mice lacking GPIHBP1. We reasoned that GPIHBP1 could play an important role in lipoprotein lipase biology. We quickly discovered that GPIHBP1 is expressed in capillary endothelial cells and that it binds lipoprotein lipase (2). We went on to prove that GPIHBP1 captures lipoprotein lipase from within the interstitial spaces and shuttles it across endothelial cells to its site of action along the luminal surface of capillaries (3). In GPIHBP1 knockout mice, lipoprotein lipase remains stranded in the interstitial spaces and never reaches the capillary lumen. That observation showed that GPIHBP1 is a [lipoprotein lipase] transporter, solving a longstanding mystery in the field.

PNAS: You mentioned other people putting this mystery to the side. Why do you think it continued to claim your attention?

Young: I first became interested in triglyceride metabolism because, as a medical student, one of my professors was Roy Vagelos, a lipid biochemist and National Academy



Stephen G. Young. Image credit: Anne Beigneux (photographer).

member who went on to become the CEO at Merck. He taught me about the function of lipoprotein lipase, and his lectures on lipid metabolism were memorable. I've been interested in lipoprotein metabolism for my entire career. Following training in clinical cardiology, my interest in lipid metabolism was nurtured by training in the laboratory of Joseph Witztum at the University of California, San Diego.

It was obvious from the knockout mice that GPIHBP1 played a crucial role in the function of lipoprotein lipase in triglyceride metabolism. We knew immediately that it was an opportunity to jump on.

PNAS: What makes proteins and their functions unique is their structure. What distinction in the structure of GPIHBP1 enables it to shuttle lipoprotein lipase?

Young: GPIHBP1 is a member of a protein superfamily, generally called the Ly6/uPAR or LU superfamily. In mammals, there are 25 or 30 Ly6/uPAR proteins, which serve a wide variety of functions. Each Ly6/uPAR protein contains at least one cysteine-rich, three-fingered LU domain that functions to bind a ligand. GPIHBP1's LU domain binds lipoprotein lipase in a glove-like fashion. GPIHBP1 is unique within the Ly6/uPAR superfamily in having a long, intrinsically disordered acidic domain.

PNAS: Tell us more about this acidic domain.

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Young: The acidic domain has three functions, all important for triglyceride metabolism. Michael Ploug, a magnificent scientist from Denmark, has been helpful in deciphering these functions. First, we found that the acidic domain hovers, by electrostatic forces, over a large basic patch on the surface of lipoprotein lipase; this interaction protects the structural integrity of lipoprotein lipase and preserves its enzymatic activity. In the absence of GPIHBP1's acidic domain, lipoprotein lipase is susceptible to unfolding and loss of activity. Second, the acidic domain accelerates the capture of lipoprotein lipase. We imagine that GPIHBP1's acidic domain acts as a "windshield wiper" to sweep up lipoprotein lipase from within the interstitial spaces. Third, we showed that the acidic domain is crucial for the transport of lipoprotein lipase across capillary endothelial cells. In the absence of GPIHBP1's acidic domain, lipoprotein lipase is trapped on the outer surface of capillaries by electrostatic interactions between lipoprotein lipase's basic patch and heparan sulfate proteoglycans (HSPGs). GPIHBP1's acidic domain functions as a molecular sheath for lipoprotein lipase, preventing HSPG interactions and freeing LPL to move to the capillary lumen (4).

The fact that the acidic domain preserves the structure and activity of lipoprotein lipase allowed us to make another important advance in the field: solving the structure of lipoprotein lipase. For three decades, scientists had tried to crystallize lipoprotein lipase, but they consistently failed, almost certainly because of lipoprotein lipase's instability. Because GPIHBP1 stabilizes the structure of lipoprotein lipase, we suspected that it might be possible to crystallize a GPIHBP1–lipoprotein lipase complex. In a collaboration with Gabriel Birrane, we did just that, and we solved lipoprotein lipase's structure (5). Deciphering the structure allowed us to define the molecular interactions between the two proteins and to make sense of lipoprotein lipase and GPIHBP1 mutations that cause chylomicronemia.

PNAS: Your background is in medicine. What are the clinical implications of these findings?

Young: We found, with Katsuyuki Nakajima, a clinical pathologist from Japan, that some "acquired cases" of chylomicronemia appearing later in life are caused by autoantibodies against GPIHBP1. These autoantibodies cause chylomicronemia by abolishing the ability of GPIHBP1 to bind lipoprotein lipase and transport it into capillaries. Patients with GPIHBP1 autoantibodies are often quite sick, with extremely high plasma triglycerides and debilitating bouts of acute pancreatitis. In a small group of patients, we found that an immunosuppressive drug can eliminate GPIHBP1 autoantibodies and normalize plasma triglyceride levels (6). Helping these patients has been gratifying. We now receive emails from around the world asking for our help in screening blood samples for GPIHBP1 autoantibodies.

PNAS: Do you think your training and certification in cardiology influenced your interest in triglyceride metabolism? Obviously, fat and heart health are closely linked.

Young: After my cardiology training, I was going to head out to private practice, but doing a year of research was a requirement of my fellowship program. I started research, and then I simply didn't stop. In recent years, I have lost my close connection with clinical cardiology, but I remain a physician at heart, and my clinical interests continue to fuel my research efforts. People talk about bench-to bedside research, and I think our GPIHBP1 autoantibody story represents a good example of that. But what's driven my career has been going from bedside to bench. A lot of what we've done has been identifying a protein with a role in lipid metabolism and then trying to understand how it works. Identifying a new disease and finding a treatment is gratifying, but equally gratifying for me is trying to understand how a protein works in human physiology.

1. S. G. Young *et al.*, A protein of capillary endothelial cells, GPIHBP1, is crucial for plasma triglyceride metabolism. *Proc. Natl. Acad. Sci.* **119**, e2211136119 (2022).
2. A. P. Beigneux *et al.*, Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 plays a critical role in the lipolytic processing of chylomicrons. *Cell Metab.* **5**, 279–291 (2007).
3. B. S. J. Davies *et al.*, GPIHBP1 is responsible for the entry of lipoprotein lipase into capillaries. *Cell Metab.* **12**, 42–52 (2010).
4. W. Song *et al.*, Electrostatic sheathing of lipoprotein lipase is essential for its movement across capillary endothelial cells. *J. Clin. Invest.* **132**, e157500 (2022).
5. G. Birrane *et al.*, Structure of the lipoprotein lipase–GPIHBP1 complex that mediates plasma triglyceride hydrolysis. *Proc. Natl. Acad. Sci.* **116**, 1723–1732 (2018).
6. A. P. Beigneux *et al.*, Autoantibodies against GPIHBP1 as a cause of hypertriglyceridemia. *N. Engl. J. Med.* **376**, 1647–1658 (2017).